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Supplement Article

VIII. New markers in peripheral T-cell lymphomas: more entities or more confusion?

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Introduction

Peripheral T-cell lymphomas (PTCLs) are heterogeneous and uncommon malignancies featuring an aggressive clinical course and a mostly poor outcome with current treatment strategies [1]. Recent developments using genome-wide molecular profiling methods have provided novel insights into their pathobiology and identified new markers with diagnostic, prognostic and/or therapeutic implications. Cell lineage and differentiation [markers of γδ or natural killer (NK) lineage, cytotoxic immunophenotype, follicular helper T-cell differentiation] account in part for the tumour biology and represent useful features to refine the diagnostic and prognostic stratification of the patients. Novel genetic aberrations are being discovered (*ITK-SYK* translocation, *IRF4/MUM1* and *DUSP22* rearrangements, *IDH2*, *TET2*, *STAT3* and *JAK3* point mutations), that may serve as diagnostic genetic markers. Deregulated molecules within oncogenic pathways (NF-κB, Syk, PDGFRα) and immunoreactive cell-surface antigens (CD30, CD52) are being exploited as potential targets for the development of novel therapies.

Biomarkers of cell lineage/differentiation (Table 1)

The precise cellular origin of many PTCL entities remains poorly characterized, likely in relationship to the complexity and functional diversity of normal T-cell differentiation, but also functional overlap and plasticity between T-cell and NK-cell subsets. Accordingly, there is pronounced phenotypical variability within distinct PTCL entites [2].

Markers of αβ, γδ T-cell and NK-cell lineages: plasticity among cytotoxic lymphomas [2]

While the vast majority of mature T lymphocytes are αβ T cells (of the adaptive immune system), γδ T cells together with NK cells and a minor subset of αβ T cells participate in the innate immune responses as a first-line of defence. In addition to regulatory functions through release of various cytokines, these cells exert cytotoxic properties through recognition by their membrane-associated killer cell immunoglobulin-like receptors (KIRs), of major histocompatibility complex class I molecules on the target cells. Because KIRs comprise multiple isoforms, a restricted KIR repertoire can be used as a surrogate marker of clonal cellular expansion. This feature has proven particularly useful for differentiating reactive from neoplastic expansions of T-cell large granular lymphocytes (T-LGL) and of NK cells by flow cytometry. Restricted KIR expression is also demonstrated in extranodal NK/T-cell lymphoma, nasal type (NKTCL), hepatosplenic T-cell lymphoma (HSTL) and enteropathy-associated T-cell lymphoma (EATL).

Antibodies recognizing epitopes specific to both αβ and γδ T cells in routinely processed tissues are now available. Reflecting the paucity and distribution of normal γδ T cells, γδ PTCLs comprise a heterogeneous group of rare neoplasms, most often extranodal and aggressive (Table 1). These comprise most HSTL, primary cutaneous γδ T-cell lymphoma, minor subsets of other entities (T-LGL, NKTCL, EATL) as well as a small minority of PTCL, not otherwise specified (PTCL, NOS).

Hepatosplenic T-cell lymphoma initially defined by its γδ derivation (although rare αβ cases exist), occurs predominantly in young adults sometimes in the setting of

Table 1. Current WHO classification, postulated cell of origin and cytotoxic phenotype of peripheral T-cell and NK-cell lymphomas (adapted from Bisig *et al.* [2])

Predominant presentation	PTCL entity	Postulated cell of origin	Cytotoxic phenotype
Disseminated/leukaemic	T-cell prolymphocytic leukaemia	Tαβ	Non-cytotoxic
	T-cell large granular lymphocytic leukaemia	Tαβ (more rarely Tγδ)	Cytotoxic (A)
	Chronic lymphoproliferative disorders of NK cells[1]	NK (°)	Cytotoxic (A)
	Aggressive NK-cell leukaemia	NK	Cytotoxic (A)
	Systemic EBV-positive T-cell lymphoproliferative disease of childhood	Tαβ	Cytotoxic (A)
	Adult T-cell leukaemia/lymphoma	Tαβ (Treg)	Non-cytotocic
Extranodal	Extranodal NK/T-cell lymphoma, nasal type	NK (more rarely Tγδ or Tαβ)	Cytotoxic (A)
	Enteropathy-associated T-cell lymphoma (°°)	Tαβ (more rarely Tγδ)	Cytotoxic (A)
	Hepatosplenic T-cell lymphoma	Tγδ (more rarely Tαβ)	Cytotoxic (NA)
Cutaneous	Subcutaneous panniculitis-like T-cell lymphoma	Tαβ	Cytotoxic (A)
	Mycosis fungoides	Tαβ (mostly CD4)	
	Sézary syndrome	Tαβ (mostly CD4)	
	Primary cutaneous CD30+ T-cell lymphoproliferative disorders	Tαβ (mostly CD4)	Cytotoxic (A)
	Primary cutaneous anaplastic large cell lymphoma	Tαβ (CD4)	Cytotoxic (A)
	Lymphomatoid papulosis	Tαβ (CD4)	Cytotoxic (A)
	Primary cutaneous γδ T-cell lymphoma	Tγδ	Cytotoxic (A)
	Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma[1]	Tαβ (CD8)	Cytotoxic (A)
	Primary cutaneous CD4+ small/medium T-cell lymphoma[1]	Tαβ (CD4, T_{FH})	Non-cytotoxic
	Hydroa vacciniforme-like lymphoma	Tαβ (rarely NK)	Cytotoxic (A)
Nodal	Peripheral T-cell lymphoma, not otherwise specified	Tαβ (CD4 > CD8, a subset T_{FH}, rarely Tγδ)	Variable, a small subset cytotoxic (A)
	Angioimmunoblastic T-cell lymphoma	Tαβ (CD4, T_{FH})	Non-cytotoxic
	Anaplastic large-cell lymphoma, ALK-positive	Tαβ (Th2?)	Cytotoxic (A)
	Anaplastic large-cell lymphoma, ALK-negative[1]	Tαβ (Th2?)	Cytotoxic (A)

WHO, World Health Organization; ALK, anaplastic lymphoma kinase; EBV, Epstein–Barr virus; NK, natural killer. Cytotoxic (A) = Activated cytotoxic phenotype, that is expression of perforin and/or granzyme B in addition to TIA-1; Cytotoxic (NA) = Non-Activated cytotoxic phenotype, that is expression of TIA-1 only.
[1]Provisional entities. (°) most likely the NK variant of T-LGL (°°) EATL type 1 more frequently of Tαβ lineage, EATL type 2 more frequently Tγδ

chronic immune deregulation. This disease, which portends an extremely poor outcome, is characterized by hepatosplenomegaly, cytopenias, a predominantly sinusoidal distribution of the neoplastic cells in the spleen, liver and bone marrow and most cases feature an isochromosome 7q.

Among cutaneous T-cell lymphomas, those of γδ derivation, irrespective of the histological pattern, have been grouped under a single entity. γδ PTCLs also can present in mucosal sites and appear clinically and morphologically heterogeneous, comprising cases that have the characteristic clinicopathologic features of NKTCLs and EATL (especially type II).

Accordingly, recent gene expression studies have evidenced that, whereas HSTLs feature a distinct molecular signature grouping αβ and γδ cases [3], non-hepatosplenic γδ PTCLs comprise cases clustering with NKTCLs. Conversely, whereas most NKTCLs appear to originate from NK-cells, up to 38% have a γδ and more rarely αβ phenotype, therefore emphasizing plasticity in term of cell derivation in these cytotoxic neoplasms, most likely reflecting the importance of cell function and cell tropism. In addition, NKTCL irrespective of NK versus T-cell derivation, have a homogeneous molecular signature and distinctively show high levels of Granzyme H transcripts. With the exception of cutaneous γδ lymphoma, no clear difference in clinical features and prognosis has yet been identified between the αβ and γδ counterparts of each subtype.

Within the PTCLs with a common nodal presentation, an activated cytotoxic profile is characteristic of anaplastic large cell lymphomas (ALCL) and of a small group of PTCL, NOS category identified through a distinct molecular signature, which is associated to a very poor prognosis.

Follicular helper T (T_{FH})-cell markers characterize a large subset of peripheral T-cell lymphomas [4]

Considering that the majority of PTCLs are CD4+, and that normal CD4+ T-cells comprise several functionally different subsets (Th1, Th2, Th17, T_{FH}, Treg), it is noteworthy

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that only minor subsets of PTCLs seem to arise from the Th1, Th2, Th17 subsets [5]. By contrast, a large proportion of PTCLs appear related to follicular helper T-cells (T_{FH}), which constitute a minor subset normally residing in germinal centres and acting as critical regulators of B-cell immune responses. Indeed, an essential advance in the histogenetic understanding of PTCLs was the recent identification of the T_{FH} as the cell of origin of angioimmunoblastic T-cell lymphoma (AITL), one of the most prevalent PTCL entities, which is defined by a constellation of clinical symptoms, pathologic features, frequent hypergammaglobulinemia and autoimmune manifestations. T_{FH} cells differ from other T-cell subsets by the expression of the transcription factors BCL6 and c-MAF, the cell-surface molecules PD-1/CD279, ICOS and CD200, the adaptor molecule SAP, the CXCL13 chemokine and its receptor CXCR5 and cytokines, especially IL-21. Demonstration of a T_{FH} phenotype is a helpful adjunct to support the diagnosis of AITL, in morphologically challenging cases. However, around one third of nodal lymphomas classified as PTCLs, NOS also express T_{FH}-cell markers and/or show some AITL-like histologic features and/or show enrichment in the T_{FH} gene signature, questioning the borders of the spectrum of AITL. Other PTCL subsets expressing T_{FH}-cell markers include the follicular variant of PTCL, NOS (PTCL-F) in which the lymphoma cells develop in relationship to B-cell follicles raising the question of a possible relationship with AITL and primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma, a provisional entity often presenting as a solitary skin nodule with an indolent clinical course.

Genetic aberrations and deregulated pathways: a road to diagnostic biomarkers and to novel targeted therapies (Table 2) [5,6]

Recurrent chromosomal translocations

For many years, translocations involving the anaplastic lymphoma kinase (*ALK*) gene (@2p23) have been basically the sole recurrent translocation identified in PTCL, and ALK-positive ALCL currently represents the only PTCL entity defined by a genetic lesion. Today, this scenario is changing rapidly, as novel recurrent genetic alterations are being discovered in PTCLs, most recently as a result of next generation sequencing technologies, and their list is expected to be growing in the future.

ALK rearrangements – In ALK-positive ALCL, *ALK* translocations lead to expression of ALK fusion proteins with oncogenic properties, resulting in the constitutive activation of ALK and in the engagement of multiple signalling pathways, including the JAK3/STAT3 and the PI3K/Akt pathways. ALK testing is crucial to establish the diagnosis, which is critical for the distinction from other CD30+ PTCLs (ALK-negative ALCL and a subset of PTCL, NOS CD30+), in view of the better clinical outcome of ALK-positive ALCL. From a therapeutic prospective, crizotinib, a small-molecule ALK inhibitor, has yielded promising preliminary results in patients refractory to standard chemotherapy regimens.

ITK-SYK translocation – The t(5;9)(q33;q22) translocation involving breaks within *ITK* @5q and *SYK* @9q generates an ITK-SYK fusion protein, which is a catalytically active tyrosine kinase (TK) with transforming properties demonstrated *in vitro* and in transgenic mouse models. This translocation occurs predominantly in association with PTCL-F, but overall in <20% of the cases, hence the diagnostic utility of detection *ITK-SYK* fusion by FISH assays is limited. Interestingly, inhibition of SYK is being investigated as a novel potential therapeutic option in PTCLs in general (see later), and a high sensitivity of tumours with *ITK-SYK* fusion may be expected.

Rearrangements involving the 6p25.3 locus (*IRF4 or DUSP22*) – These have been recently reported in approximately 20% of systemic and 30% of cutaneous ALK-negative ALCLs. Albeit involving the 6p25.3 locus, the breaks actually affect different genes, corresponding to *IRF4* in about one third of the cases and to *DUSP22* in another fraction of the cases. *IRF4* translocation partner is mostly unknown. When the rearranged gene is *DUSP22* (encoding a dual-specificity phosphatase that inhibits T-cell receptor signalling), its partner locus is located at 7q32.3 in around half of the cases, in close proximity of the *FRA7H* fragile site and the microRNA-coding *MIR29* gene. This t(6;7)(p25.3;q32.3) entails downregulation of *DUSP22* and overexpression of *MIR29*, suggesting that *DUSP22* might function as a tumour suppressor and *MIR29* as an oncogene. Because 6p25.3 locus rearrangements appear specific to ALK-negative ALCLs, FISH-based assays may be helpful for the diagnosis, especially of cutaneous CD30+ T-cell lymphoproliferations; in this setting, demonstration of a 6p25.3 translocation is almost specific for primary cutaneous ALCL.

Rearrangements involving p53-related genes – recurrent abnormalities involving several p53-related genes have been recently evidenced in PTCLs. In particular, novel *TP63* rearrangements encoding fusion proteins homologous to ΔNp63, a dominant-negative p63 isoform that inhibits the p53 pathway are seen in around 6% of PTCLs and associated with inferior overall survival. Because *TP53* mutations are rare in PTCL, these findings suggest that a constellation of alternate genetic abnormalities may contribute to disruption of p53-associated tumour suppressor function in PTCLs [7].

Others – Finally, a recent study identified CD28-ICOS fusion transcripts in some cases of AITL, a finding of interest in view of the role of these costimulatory molecules in the interaction between T_{FH} and B cells [8]

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Table 2. Summary of the biomarkers discussed in this review and their clinical relevance in the diagnosis, prognosis and/or treatment of peripheral T-cell lymphoma entities

Biomarkers	Associated PTCL entities	Clinical significance
Lineage / differentiation markers		
TCRγ and TCRδ chains	HSTL Primary cutaneous γδ TCL Other non-HS γδ PTCLs	Diagnosis, Prognosis: γδ PTCLs are highly aggressive
NK-cell receptors: KIRs	NK-cell lymphoproliferations, T-LGL (restricted KIR repertoire) Sézary syndrome (aberrant expression of CD158k/ KIR3DL2)	Diagnosis
Cytotoxic molecules:		Diagnosis1, Prognosis: cytotoxic PTCLs,
TIA-1, perforin, granzyme B, granzyme H		NOS have poorer outcome
T_{FH}-cell markers: CXCL13,	AITL PTCL-F	Diagnosis
PD-1, ICOS, CD200, SAP, Bcl-6, c-Maf	Primary cutaneous CD4+ small/ medium TCL	
Cell-surface markers		
CD30	ALK + and ALK-ALCL Subset of PTCL, NOS Primary cutaneous CD30+ T-cell lymphoproliferative disorders	Diagnosis, Therapy: brentuximab vedotin targets CD30
CD52	Subset of AITL, PTCL, NOS, NKTCL, ATLL Minority of ALCL	Therapy: alemtuzumab targets CD52
Chromosomal translocations		
ALK rearrangement	ALK + ALCL	Diagnosis, Prognosis: ALK + ALCLs have better outcome
ITK-SYK translocation	Subset of PTCL-F	Diagnosis, Therapy: fostamatinib inhibits SYK activity
IRF4 or *DUSP22* rearrangement	Subset of systemic and cutaneous ALK-ALCL	Diagnosis
Other genetic aberrations		
STAT3 mutations	T-LGL, chronic NK-cell LPD	Diagnosis, Therapy?
TET2, *IDH2*, *DNMT3* mutations	AITL, PTCL,NOS 'TFH-like' (*TET2*, *DNMT3*)	Diagnosis?
JAK3 mutations	NKTCL	Diagnosis?, Therapy?
Signalling pathways		
NF-κB	ATLL NKTCL Cutaneous TCL PTCL, NOS, AITL, ALK-ALCL	Prognosis: 'NF-κB high' PTCLs have better outcome Therapy: bortezomib blocks NF-κB pathway
SYK	Majority of PTCLs Subset of CD30+ PTCLs	Therapy: *f*ostamatinib inhibits SYK activity
PDGFRα	PTCL, NOS AITL NKTCL	Therapy: imatinib inhibits PDGFRα activity

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukaemia/lymphoma; HSTL, hepatosplenic T-cell lymphoma; KIR, killer cell immunoglobulin-like receptor; NK, natural killer; NKTCL, extranodal NK/T-cell lymphoma; non-HS, non-hepatosplenic; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; PTCL-F, follicular variant of PTCL, NOS; TCL, T-cell lymphoma; TCR, T-cell receptor; T_{FH}, follicular helper T-cell; T-LGL, T-cell large granular lymphocytic leukaemia.

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Other chromosomal alterations

Deletion at 6q21-25 and *isochromosome 7q* are the most recurrent chromosomal aberrations in NKTCL and HSTL, respectively, whereas *gains at 9q31* and *partial trisomy 1q22-q44* represent the most frequent aberrations in EATL (type I). The 6q deleted region contains four candidate tumour suppressor genes, that is *PRDM1*, *ATG5*, *AIM1* and *HACE1*, with decreased expression confirmed in NKTCLs [9]. As several of these genes appear to be inactivated through methylation, the potential use of demethylating agents in refractory patients might be suggested.

Point mutations – Recently, targeted or whole-exome sequencing studies identified several somatic mutations associated with specific PTCL entities. *STAT3 mutations* were identified in approximately one third of patients with either T-LGL or chronic lymphoproliferative disorders of NK-cells, therefore unifying the pathogenesis of both diseases [10]. These mutations may help to distinguish these indolent malignant proliferations from reactive expansions. In addition, treatment with STAT3 inhibitors appears a promising therapeutic option by inducing the accelerated apoptosis of leukemic NK or T cells. *JAK3* somatic activating mutations have been reported in around one third of NKTCL and are likely to be implicated in the constitutive activation of the JAK-STAT pathway in this entity. These findings may have therapeutic implications as JAK inhibitors resulted in reduced cell viability and increased apoptosis of NKTCL cell lines [11].

Recent works have evidenced recurrent point mutations in genes encoding for enzymes involved in the epigenetic control of transcription, especially DNA methylation (*TET2*, *IDH2* and *DNMT3*) [12]. More specifically, *TET2* mutations are identified in about half of AITL and in a proportion of PTCL, NOS, especially in those expressing T_{FH} markers and/or showing features reminiscent of AITL; *TET2* mutations are associated with advanced-stage disease, high international prognostic index scores, and a shorter progression-free survival. *IDH2* mutations were identified in 20–40% of AITL, but not in other PTCL entities, whereas *DNMT3A* mutations are found in about 10% of PTCL patients, often in association with *TET2* mutations. In a few patients, there is evidence that the mutations are acquired in an early hematopoietic progenitor. There is also suggestion of an oncogenic cooperation between *TET2* and *DNMT3A* mutations that may involve deregulation of the cytosine methylation and demethylation processes. These data may also have diagnostic value and clinical implications, as they may offer rationale to consider demethylating agents in the treatment of AITL or PTCL, NOS patients with these mutations.

Deregulated signalling pathways and therapeutic implications

Molecular studies have evidenced extensive deregulation of several signalling pathways—apoptosis, cell cycle, cell adhesion, matrix remodelling and chemoresistance—in PTCLs in comparison with normal cell counterparts entailing prognostic and/or therapeutic implications. NF-κB pathway, which has been found constitutively activated in adult T-cell leukaemia/lymphoma and in ENKTL—likely mediated by the Epstein–Barr virus and HTLV1 infection, respectively—with more controversial results in other PTCL entities, is targetebable by NF-κB-blocking compounds such as bortezomib (a proteasome inhibitor) with some clinical efficacy. Several studies have emphasized aberrant TK signalling in PTCLs. Aberrant SYK expression has been demonstrated as a feature common to many PTCLs (belonging to several PTCL entities including HSTL and CD30+ PTCLs) with constitutive kinase activity. The efficacy of SYK inhibitors in limiting proliferation and inducing apoptosis in T-lymphoma cell lines *in vitro* is now translated into an ongoing trial with fostamatinib in PTCL patients.

In addition, several studies have shown overexpression and constitutive activation of *PDGFRA* in several PTCL entities comprising PTCL, NOS, AITL and NKTCL, likely to be sustained by an autocrine stimulation. Notably, *in vitro* studies have demonstrated the sensitivity of malignant T-cells to imatinib mesylate, a TK inhibitor with known anti-PDGFRα activity. Altogether, these data point towards TK inhibitors as new candidates for targeted treatment strategies in PTCLs patients.

Finally, several PTCL entities, including NKTCL, T-LGL and ALK + ALCL, show constitutive activation of STAT3, resulting in growth advantage and resistance to apoptosis. This offers a rationale for using compounds/inhibitors targeting the JAK-STAT pathway in those patients.

Cell-surface biomarkers relevant to therapy [2,5]

In view of the 'success story' of the anti-CD20 monoclonal antibody rituximab, which has revolutionized the treatment and outcome of patients with B-cell lymphomas, efforts have been undertaken to develop therapeutic antibodies targeting cell-surface molecules in PTCLs. Among these, CD30 and CD52 have so far revealed as the most promising targets. Other humanized antibodies such as those targeting the chemokine receptor CCR4 expressed in adult T-cell leukaemia/lymphoma and others PTCLs, are tested in clinical trials.

CD30

Strong and homogeneous expression of CD30 is a hallmark feature of ALCLs and of the primary cutaneous CD30+ T-cell lymphoproliferative disorders. A subset of cases in virtually all PTCL entities may also express CD30 but at variable

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and generally lower levels. Owing to its minimal expression in reactive tissues, CD30 is theoretically an optimal target for therapy. Recently, brentuximab vedotin (SGN-35) has been developed, an anti-CD30 antibody linked to an antitubulin agent inducing cell cycle arrest and apoptosis. Early clinical trials demonstrated remarkable clinical responses in relapsed or refractory CD30+ lymphomas with limited toxicity. The potential benefits of incorporating this promising agent into established chemotherapy regimens are being investigated, including as front-line therapy and for patients with non-anaplastic CD30+ PTCLs such as CD30+ PTCLs, NOS, bearing a much poorer prognosis with conventional treatment approaches.

CD52

The presence of CD52 antigen on malignant lymphocytes has been exploited therapeutically as the target of alemtuzumab (Campath-1H), a humanized anti-CD52 monoclonal antibody inducing complement-mediated cell lysis, antibody-dependent cell cytotoxicity and apoptosis. Several clinical trials have demonstrated the activity of alemtuzumab against PTCLs. Promising responses have been observed in association with conventional polychemotherapy regimens, although frequently with major hematologic toxicity and infectious complications.

An open question remains the delineation of the histological subtypes that could more efficiently be targeted by alemtuzumab as around half of PTCL patients present a consistent downregulation of CD52. Further studies are warranted to determine the predictive value of CD52 detection (by immunohistochemistry and/or flow cytometry) in PTCL samples.

Conclusion

Despite insights in the determination of cell counterpart for several PTCL entities, plasticity observed in term of cell derivation especially in some extranodal entities, may lead to some confusion in the use of histogenetic markers (such as NK, γδ and αβ) for their definition. Novel molecular abnormalities implying deregulation of common pathways, are being discovered, that are more or less specific of PTCL entities or have a more widespread distribution, suggesting that they may represent candidate targets for novel drugs with a range of applications extending beyond single pathological entities. It is likely that the current classification will change in the future to incorporate novel discoveries and in particular the PTCL NOS category needs to be sorted out into biologically relevant subgroups.

Conflict of Interest

The authors have no competing interest.

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